REMARKS

Objection to the Specification and Rejection of Claims 36-53 Under 35 U.S.C. § 112, First Paragraph (New Matter):

The Examiner has objected to the specification and rejected Claims 36-53 under 35 U.S.C. § 112, first paragraph, contending that the claims add new matter. Specifically, the Examiner asserts that the present claims represent a departure from the specification as originally filed. The Examiner contends that the word "phospho-antigen" is mentioned in the specification on page 62 two times, and that isoprenylpyrophosphate is listed as an example of a phospho-antigen. The Examiner contends that the specification does not contemplate any of the newly added claims, but rather, the specification teaches the use of phosphoantigen and isoprenylpyrophosphate for activation of γδ T cells. The Examiner asserts that the specification never contemplated using any phosphoantigen, nor using isoprenylpyrophosphate in particular.

The rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The analysis of whether the specification complies with the written description requirement should be conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) (emphasis added). See also MPEP 2163II(A)(2). With this standard in mind, the rejection is discussed.

Applicants specifically traverse the Examiner's assertion that the specification does not contemplate using any phosphoantigen in the presently claimed method. Page 31, lines 21-24 state the following:

> "For the activation of γδ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the

research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)."

Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification) for use in activation of γδ T cells, and provides a reference to the knowledge of such phosphoantigens in the art. The Examiner asserts that the specification is devoid of a teaching to use phosphoantigens in the claimed method, but this is not accurate. To the contrary, a careful reading of the specification reveals that this paragraph is one in a series of paragraphs beginning on page 25, line 5, and ending on page 33, line 10, which describe a variety of agents that can be used to act on γδ T cells and increase the proliferation, activation/biological activity, and/or survival of γδ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory γδ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal (emphasis added). Indeed, referring to page 25, lines 5-20, the specification teaches:

> "In one embodiment, the method of the present invention includes the use of a variety of agents (i.e., regulatory compounds) which, by acting on γδ T cells, increase the proliferation, activation/biological activity, and/or survival of γδ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory γδ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal. Such agents are generally referred to herein as γδ T cell agonists. According to the present invention, a γδ T cell agonist is any agent which increases, typically by direct action on the cell, the proliferation, activation/biological activity, and/or survival of γδ T cells, and includes agents which act directly on the γδ T cell receptor. A γδ T cell agonist, as referred to herein, can further include, for example, compounds that are products of rational drug design, natural products, and compounds having partially or fully defined γδ T cell stimulatory properties. A γδ T cell agonist can be a protein-based compound, a carbohydrate-based compound, a lipid-based compound, a nucleic acid-based compound, a natural organic compound, a synthetically derived organic compound, an antibody, or fragments thereof. A variety of known γδ T cell agonists are described below and all are encompassed by the present invention."

The specification then goes on to list a variety of agents that can be used in the method of the invention, paragraph by paragraph, which includes the paragraph on page 31 and the reference to phosphoantigens, clearly identifying this agent as useful in the method of the invention.

Accordingly, it is completely incorrect to state that the specification never contemplated using phosphoantigens in the claimed method.

If the Examiner is objecting to the use of the spelling "phospho-antigen" instead of "phosphoantigen", this is a mere difference in the spelling of the term. However, given the clear definition in the specification of "antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)", as discussed above, it is clear to one of skill in the art that these are alternate spellings of the same word. However, in order to alleviate this portion of the Examiner's concerns regarding this term, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter. Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). The mere inclusion of dictionary or art recognized definitions known at the time of filing an application would not be considered new matter. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Odd*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

In view of the foregoing remarks, the withdrawal of the rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Objection to the Specification and Rejection of Claims 36-53 Under 35 U.S.C. § 112, First Paragraph (Enablement):

The Examiner has objected to the specification and rejected Claims 36-53 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner states that the specification is enabling for a method to reduce airway hyperresponsiveness by increasing γδ T cell action through the administration of tumor necrosis factor-α (TNF-α). However, the Examiner contends that the specification does not enable a method to reduce airway hyperresponsiveness by increasing γδ T cell action through the administration of a phosphoantigen, including isoprenylpyrophosphate. The Examiner asserts that the method is not supported by the disclosure or the examples, and more particularly, the Examiner states that the

use of a phosphoantigen to reduce airway inflammation "would not work". In support of this conclusion, the Examiner cites Cendron et al. as describing phosphoantigens as being "mycobaterial non-peptide antigens" that require IL-2 to promote proliferation *in vitro* and *in vivo*, and that a strong initial Th1 response to phosphoantigens was seen in monkeys, but was followed by an anergic/hyporesponsive state where T cells are unresponsive to the antigen. The Examiner contends that the same response was shown in Sicard with another phosphoantigen, BrHPP. The Examiner contends that Sicard teaches that a transient γδ T cell response returns to baseline within 10-15 days and concludes that the prior art shows that γδ T cells do not exhibit sustained activation in response to phosphoantigens for any therapeutic benefit. Accordingly, the Examiner contends that it would require undue trial and error to practice the claimed invention.

The rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). With this standard in mind, the rejection raised by the Examiner is discussed below.

Applicants submit that the Examiner is incorrect in making the statement that the claimed method "would not work". This is not at all supported by the specification, the knowledge in the art at the time of the invention, or the evidence of record. First, Applicants submit that it was known in the art at the time of the invention that phosphoantigens are a class of agents that can activate γδ T cells. In support of this position, enclosed herewith is a publication by Lang et al. (1995, *J. Immunol.* 154:5986-5994) which shows that phosphoantigens are known to activate γδ T cells and that activated γδ T cells are known to induce a IFN-α production (see, *e.g.,* abstract

and Introduction, where the phosphorylated molecules designated "TUBag" are phosphoantigens). Publications of Belmant et al. and Espinosa et al. (discussed below) are also enclosed herewith, and are additional evidence that it was known at the time of the invention that phosphoantigens could activate γδ T cells. The present inventors have demonstrated that activation of γδ T cells will inhibit airway hyperresponsiveness (AHR), and these publications show that phosphoantigens are one agent that will activate γδ T cells. Indeed, the Examiner also provides publications demonstrating that phosphoantigens will activate γδ T cells (see discussion below). Therefore, phosphoantigens are reasonably expected to be one agent with which the claimed method of the present invention can be performed.

With regard to the publications provided by the Examiner of Cendron et al. and Sicard et al., Applicants submit that these publications do not demonstrate, as the Examiner asserts, that the claimed invention "would not work". Each of Cendron et al. and Sicard et al. in fact demonstrate that phosphoantigens activate γδ T cells. Indeed, Sicard et al. conclude that administration of the phosphoantigen, BrHPP, represents a promising immunotherapeutic strategy for the induction of systemic Th1 cytokines and massive expansion of γδ T cell subset (see abstract, for example). Sicard et al. also note that their results only account for the "visible pool" of γδ T cells (in the periphery) and that the use of IL-2 may result in different means of activation/differentiation of γδ T cells than when they do not amplify (see page 5478, col. 2). It is clear that Sicard et al. do not conclude that the use of phosphoantigens to activate γδ T cells is ineffective and therefore, the Examiner's assertion to the contrary is not supported by the evidence of record. Cendron et al. also conclude that better recall responses to γδ T cells will be achieved, noting contrary results when the antigen is presented in a different form (see page 561, col. 2).

In addition, Applicants submit that for the purposes of controlling AHR, it is not necessary and in fact, not desirable, to have continuous, sustained activation of γδ T cells in response to phosphoantigens, nor continuous stimulation of Th1 type cytokines, and that a response that is transient or controllable is not a downside to use of phosphoantigens nor is it any indication that the claimed method would not work. The use of phosphoantigens in the claimed method is intended to prevent or reduce AHR when it occurs and it is not desirable to have a continuous γδ activation. Indeed, it is generally not desirable to have continuous immune system activation when using an immunotherapeutic approach. The goals of the method can be met by a

single stimulation of γδ T cells with a phosphoantigen to prevent or reduce AHR when it occurs, and so it is perfectly acceptable for the population of γδ T cells to increase for a period of days and then return to baseline.

Moreover, once activated, γδ T cells produce significant amounts of tumor necrosis factor-α (TNF-α), and exposure of γδ T cells to phosphoantigens increases the production of TNF-α by these cells. This is demonstrated by the attached publications, which describe the ability of activated γδ T cells to produce TNF-α, including in response to activation by phosphoantigens (Ismaili et al., 2002, *Clin. Immunol.* 103:296-302; and Wang et al., 2001, *J. Immunol.* 167:6195-6201). Referring to Ismaili, page 299-300, this publication teaches that γδ T cells produce TNF-α and that BrHPP (a known phosphoantigen) "further increased this basal production of TNF-α and also induced IFN-γ secretion by γδ T cells". Wang et al. teaches (see abstract) that human γδ T cells produce TNF-α as early as 2h after antigen exposure. Wang et al. also teach (page 6195, col. 1-2) that several "lines of evidence suggest that γδ T cells participate in the immune response to microbial pathogens by producing factors such as IFN-γ and TNF-α".

TNF-α, as acknowledged by the Examiner and as previously demonstrated by Applicants, inhibits airway hyperresponsiveness in sensitized and challenged mice, *via* an effect on the activity of γδ T cells. In addition, the inventors have demonstrated that administration of TNF-α reduces airway hyperresponsiveness independently of cellular inflammation in the lung. As evidence of this statement, Applicants enclose herewith a copy of a Declaration under 37 CFR § 1.132 that was submitted by the inventors and is of record in the parent application (U.S. Patent Application No. 09/672,865). Accordingly, Applicants have shown that activation of γδ T cells can inhibit airway hyperresponsiveness (AHR), and Applicants have also previously demonstrated one such agent for activation of γδ T cells which results in the inhibition of AHR is TNF-α. Applicants further demonstrate herein that phosphoantigens can also activate γδ T cells (see above), which accordingly will be expected to inhibit AHR according to the invention. Furthermore, Applicants provide evidence herein that one result of such activation of γδ T cells by phosphoantigens is the further induction of TNF-α (see above), which as discussed has already been shown by the inventors to have a corresponding effect on γδ T cells and AHR. Taken together, this evidence demonstrates that phosphoantigens administered in the presently claimed method are reasonably expected to inhibit AHR, and that the claimed invention is fully enabled.

In view of the foregoing remarks, withdrawal of the rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Objection to the Specification and Rejection of Claims 36-53 Under 35 U.S.C. § 112, First Paragraph (Written Description):

The Examiner has objected to the specification and rejected Claims 36-53 under 35 U.S.C. § 112, first paragraph, on the basis of written description. Specifically, the Examiner contends that Applicants are in possession of a method to reduce airway hyperresponsiveness in a mammal by increasing γδ T cell action by administering TNF-α, but asserts that Applicants have not demonstrated possession of a method to reduce airway hyperresponsiveness in a mammal by increasing γδ T cell action by administering a phosphoantigen. The Examiner contends that the specification does not describe the word "phosphoantigen", but rather "phospho-antigen". The Examiner asserts that the term "phosphoantigen" describes many non-peptide compounds, including all as yet undiscovered phosphoantigens. The Examiner contends that there is no support in the specification for any species of phosphoantigen other than isoprenylpyrophosphate (IPP), and that it is further noted that throughout the literature "IPP" stands for a different molecule, namely isopentenylpyrophosphate, so it is unclear to the Examiner whether the recited compound is actually useful in the claimed invention. The Examiner contends that neither the exemplary embodiments nor the specification's general method describe the structural features common to the genus and accordingly, the Examiner contends that the specification directs those skilled in the art to figure out what a phosphoantigen looks like. The Examiner contends that the skilled artisan cannot envision all of the contemplated phosphoantigen possibilities recited in the instant claims and that conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred.

The rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the

claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998). As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met … even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084. MPEP 2163II(A)(3)(a). With this standard in mind, the rejection is now specifically addressed.

First, as discussed in detail above with respect to the new matter rejection, the specification teaches that: "For the activation of γδ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)" (Page 31, lines 21-24). Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification, which is simply an alternate spelling for the term, as discussed above) for use in activation of γδ T cells, and provides a reference to the knowledge of such phosphoantigens in the art.

To attempt to obviate the Examiner's concerns, as discussed above, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter.

Moreover, the term "phosphoantigens" was well-known to those of skill in the art at the time of the invention. As evidence of this position, enclosed herewith are two publications (Belmant et al., 2000, *FASEB* 17:1669-1670; and Espinosa et al., 2001, *Microbes and Infection* 3:645-654), both of which establish that the term "phosphoantigen" was well-known in the art at

the time of the invention, and that multiple examples of natural and synthetic phosphoantigens were known. These references also further establish that at the time of the invention, it was known that phosphoantigens could activate γδ T cells. Accordingly, the art already recognizes the structural features common to the genus of phosphoantigens and therefore, the skilled artisan does not need to "figure out what a phosphoantigen looks like". One of skill in the art is already apprised of what is a phosphoantigen, including different examples of members of the genus, and accordingly, one of skill in the art can readily envision multiple contemplated phosphoantigen possibilities recited in the instant claims. Establishment of sufficient written description does not require that Applicants describe each and every embodiment that may fall within the scope of the claims. The analysis of whether the specification complies with the written description requirement should be conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) (emphasis added). See also MPEP 2163II(A)(2). Applicants submit that the specification description is sufficient to place the inventors in possession of the claimed invention at the time of filing.

With regard to the Examiner's concern that throughout the literature "IPP" stands for a different molecule, namely isopentenylpyrophosphate, it is agreed that in the literature, isopentenylpyrophosphate is also denoted by the acronym, IPP. However, it is noted that isopentenylpyrophosphate is in fact a particular compound included in the larger family of isoprenylpyrophosphates. "Isoprenyl" is a more generic term than "isopentenyl", and in fact "prenyl" stands for a skeleton of 5n carbon atoms; however, this carbon skeleton can undergo various substitutions resulting in many different products (alcohol moiety, acid moiety, different alkyl substitutions, etc...). When n=1, then isoprenyl is isopentenyl (C5, n=1), but larger isoprenyls exist (*e.g.,* geranyl (C10, n=2), farnesyl (C15, n=3), geranylgeranyl (C20, n=4)). Therefore, one isoprenylpyrophosphate that can be used in the present invention would be isopentenylpyrophosphate.

In view of the foregoing remarks, withdrawal of the rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Applicants have attempted to address the rejections set forth in the May 3 Office Action and submit that the claims are in a condition for allowance. To expedite the prosecution of these claims, the Examiner is encouraged to contact the below-named agent at (303) 863-9700 with any remaining questions or concerns regarding the claims.

Respectfully submitted,

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